IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 10/594,864

Confirmation No. 1275

Applicant: Shinohara et al.

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TC/AU: 1632

Examiner: Magdalene K. Sgagias

Docket No.: 701067 (Client Reference No. 201548)

Customer No.: 23460

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the following sheets.

Respectfully submitted,

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REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Status of Claims

Claims 1-12, 15, and 16 are pending and are the subject of this appeal.

Summary of Claimed Subject Matter

The appealed claims are directed to a method of producing pluripotent stem cells (see the specification at, for example, page 3, line 6, through page 4, line 25).

Grounds of Rejection to be Reviewed

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nagano et al. (*Biology of Reproduction, 68*: 2207-2214 (2003)) and Matsui et al. (*Cell, 70(5)*: 841-847 (1992)).

Claim 7 is rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nagano et al., Matsui et al., and Beumer et al (*Cell Death and Differentiation, 5*: 669-677 (1998)).

Claims 8-11 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nagano et al., Matsui et al., Meng et al. (*Science, 287*: 1489-1493 (2000)), and Donovan et al. (*Current Opinion in Genetics & Development, 13*: 436-471 (2003)).

Claims 11-16 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over under Nagano et al., Matsui et al., Meng et al., Donovan et al., Kanatsu-Shinohara et al. (*Biology of Reproduction, 70*: 70-75 (2004)), and Shinohara et al. (*Proc. Natl. Acad. Sci. USA, 96*: 5504-5509 (1999)).

Reasons for Withdrawal of Rejection

For subject matter defined by a claim to be considered obvious, the differences between the claimed subject matter and the prior art must be "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate

determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

In considering whether an invention would have been obvious in view of the prior art, the prior art as a whole must be considered, including any prior references that teach away from the invention. Indeed, it is legal error not to consider such references. Here, consideration of the aforementioned *Graham* factors indicates that the present invention, as defined by the appealed claims, is unobvious in view of the cited references. This is particularly evident when proper consideration is given to Labosky et al. (*Development, 12*: 3197-3204 (1994)), which teaches away from the present invention.

As regards the scope and content of the prior art, Nagano et al. teaches culturing testis cells (e.g., spermatogonial stem cells and germ cells) from transgenic mice that express lacZ using a medium containing GDNF, LIF, bFGF, and feeder cells. The Office acknowledges that Nagano et al. does not teach isolating pluripotent stem cells from the spermatogonial stem cells; however, the Office contends that Matsui et al. suggests that isolated pluripotent embryonic stem cells from murine *primordial* germ cells in culture could be maintained on feeder layers. Therefore, the Office believes that it would have been obvious for one of ordinary skill in the art to isolate pluripotent stem cells from the testis cells of Nagano et al. given the teachings of Matsui et al. The Office relies on the remaining cited references to provide the features of the remaining dependent claims.

For purposes of the analysis here, and for the sake of argument, the level of ordinary skill can be considered to be relatively high, such that a person of ordinary skill in the art would have an advanced degree and/or several years of experience in the relevant field.

The present invention, as defined by the appealed claims, is directed to a method of producing pluripotent stem cells, which comprises culturing testis cells using a medium containing GDNF or an equivalent thereto, wherein the testis cells contain spermatogonial stem cells, and wherein the testis cells are derived from a postnatal mammal, and isolating pluripotent stem cells from the cultured testis cells.

At the time the application was filed, one of ordinary skill in the art believed that it was impossible to establish pluripotent stem cells from *postnatal* cells. As an example, Labosky et al., which is a later-published reference from the same laboratory as the authors of Matsui et al. and lists the same co-author, Brigid L. M. Hogan, reports that while pluripotent cell lines can be established from *primordial* germ cells of 8 days post coitum (p.c.) embryos and 12.5 days p.c. genital ridges, germ cells from the gonads of 15.5 days p.c. embryos and newborn mice (i.e., *postnatal* germ cells) did *not* give rise to embryonic germ cell lines under the conditions disclosed in the prior art (see, e.g., page 3199, paragraph bridging columns 1 and 2). Applicants note that Labosky et al. references experiments described in Matsui et al. Therefore, one of ordinary skill in the art would have concluded from a consideration of the prior art disclosures (including Labosky et al.) that Matsui et al. does not teach that pluripotent stem cells can be established from *postnatal* cells, as required by the appealed claims.

As described in the specification, one of the most characteristic features of pluripotent stem cells is the formation of teratomas *in vivo* (see, e.g., page 31, lines 15-26, of the specification). In contrast, germ cells form spermatogenic colonies and do not form teratomas when injected into seminiferous tubules (see, e.g., page 31, lines 26-31, of the specification).

Nagano et al. discloses that the cultured cells described therein colonize recipient seminiferous epithelium and establish spermatogenesis when the cells are transferred into seminiferous tubules (see Figs. 1-3). Nagano et al. describes that spermatogonial stem cells cultured *in vitro* retain the ability to reconstitute complete spermatogenesis and produce spermatozoa (see Fig. 2). Additionally, Nagano et al. describes that GDNF had a positive effect on *in vitro* maintenance of spermatogonial stem cells (i.e., spermatogenic colonization activity) (see Fig. 3).

The reported activities of the cultured cells of Nagano et al. are *not* characteristic of pluripotent stem cells (and the assertion in the Advisory Action that "the Nagano reference embraces the claimed invention" is clearly incorrect). Accordingly, Nagano et al. did not enable one of ordinary skill in the art to obtain pluripotent stem cells, and Nagano et al. did

not provide one of ordinary skill in the art with any reasonable expectation of success in doing so with the cultured cells described in Nagano et al.

Since Matsui et al. pertains to the use of *primordial* germ cells (as opposed to *postnatal* cells), and since Labosky et al. tends to confirm that the isolation method disclosed in Matsui et al. does not result in pluripotent stem cells without the use of *primordial* germ cells (as opposed to *postnatal* cells), one of ordinary skill in the art would not have had any reason to use the methodology of Matsui et al. for the isolation of pluripotent stem cells from the cultured testis system of Nagano et al. Furthermore, even if one of ordinary skill in the art had considered using the methodology of Matsui et al. for the isolation of pluripotent stem cells on the cultured testis system of Nagano et al., there would have been no reasonable expectation of success in obtaining pluripotent stem cells. Indeed, in such an event, one of ordinary skill in the art would have followed the teachings of Matsui et al. and Labosky et al. and would have utilized *primordial* cells (rather than *postnatal* cells), thereby not replicating the present inventive method.

None of the remaining cited references provides any reason to combine the isolation method of Matsui et al. with the culturing method of Nagano et al., let alone with a reasonable expectation of success, in the manner necessary to arrive at the present invention.

The inventors recognized that pluripotent stem cells could be established from *postnatal* mammals without destruction of embryos or genetic modification using the inventive method. The inventive method circumvents the ethical problem of destroying embryos in the production of pluripotent stem cells, which is surprising and unexpected in view of the disclosures in the prior art as a whole (see, e.g., Labosky et al.). The existence of these unexpected benefits attendant the present invention rebut the obviousness position recited in the Office Action, even if the combination of the disclosures of the cited references are considered to properly establish *prima facie* obviousness.

Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the appealed claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of the cited references. Accordingly, the obviousness rejections should be withdrawn.